REMARKS

Claims 1-20 are cancelled. Claims 21-31 have been amended. New claims 32-34 have been added.

Claim Objections

Claims 23-30 were objected to for being improperly numbered. Accordingly, claims 23-30 have been renumbered 24-31. Additionally, some of the dependent claims were improperly referenced. These claims have been amended to depend from the proper preceding claims. This was a typographical error and unrelated to patentability.

Double Patenting

Claims 1-10 were rejected under the judicially created doctrine of double patenting. Claims 1 -10 have been canceled.

Claim Rejections – 35 USC §112 Written Description

Claim 22 was rejected for failing to comply with the written description requirement as allegedly containing new matter. Specifically the Examiner stated that claim 22 recited isolated cells from the list pig, rat, cow, rabbit, goat, guinea pig, prairie baboon, squirrel, monkey, chimpanzee, frog, toad, chicken, turkey and sheep, wherein the specification did not contain support for isolated cells from those animals. Paragraph [0018] of the specification discloses the preparation of transgenic animal cells from the group consisting of pig, rat, cow, rabbit, goat, guinea pig, prairie baboon, squirrel, monkey, chimpanzee, frog, toad, chicken, turkey and sheep. Isolated animal cells containing the transgene are present inherently during the *in vitro* process of creating a transgenic animal, thus claim 22 finds support in the specification for isolated cells from the above list of animals.

Claim Rejections – 35 USC §112 Enablement

Claims 1-10 were rejected for allegedly failing to enable across the full scope of the claims. Applicants respectfully disagree with the Examiner's grounds for objection. However, in order to facilitate prosecution in this case applicants have canceled claims 1-10, without prejudice or disclaimer.

Claims 21 -31 were rejected as failing to comply with the enablement requirement as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make or use the invention. Per the Examiner's recommendation during the May 4, 2004 phone interview, claims 21-31 have been amended to read upon isolated animal cells, to clarify the scope of the claims. There is support in the specification for the *in vitro* introduction of exogenous DNA into an egg or other nucleated cell. For instance, paragraph [0026] of the specification describes methods for the introduction of DNA into an isolated cell such as sperm-mediated gene-transfer, microinjection, gene-targeting, transfection, or retrovirus-mediated gene transfer.

Claims 21-31 were also rejected for failing to disclose a working example which establishes that an isolated cell whole genome comprising the enhancer element tctgagtca operably linked to any promoter expresses transcripts, wherein the level of expression is positively correlated (up-regulated) with the copy number of the transgene.

As discussed during the May 4, 2004 phone interview with the Examiner, Table 1 in the specification discloses the results of a comparison between Wild type and HS40 (mt) transgene mice. Tail vein DNA and blood from the mutant mice clearly show a linear relationship between copy number of the integrated mutant transgene and the expressed blood level of hGH. For instance, Specimen 1A of the Mutant line has a copy number of 1 of the transgene and a blood level of 530 ng/ml, Specimen 8 has 8 copies of the transgene and a 2,990 ng/ml blood level, Specimen 15 has 15 copies and 5,560 ng/ml blood hGH, and so on. No such correlation is seen in the wild type specimens, where hGH levels and copy number of the wild type element are completely unrelated.

Similarly, Table 4 of the specification discloses the linear relationship between copy number of integrated HS40 (mt) transgenes and expression of the linked hGH gene in transgenic pigs. Thus, isolated cells containing the mutant HS40 enhancer show greatly increased expression of the transcript, and this increase is copy-number related.

As also was discussed during the May 4 interview, the Zhang et al., 1993 [Mol. Cell Bio. 1394:2298-2308] paper describes the wild type HS40 element acting as a simple enhancer. In the Zhang reference, when the HS40 (mt) element was introduced on a plasmid in a transient expression system, expression of the operably-linked gene dropped 70%. In contrast, the instant invention discloses that HS40 (mt) can act as a locus control region, that is, an element that when *stably integrated into the chromosome*, causes the activity of the cis-linked promoter to *increase* in a position-independent and copy number-dependent manner. Thus the Zhang reference in fact teaches away from the current invention, which discloses that when chromosomally integrated in animal cells, the HS40 mutant enhancer causes the greatly increased, copy number-dependent expression as described in Tables 1 and 4 above.

Applicants once again thank the Examiner for his helpful comments.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **514162000120**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 18, 2004

Respectfully submitted,

By _____
Otis Littlefield
Registration No.: 48,751
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105
(415) 268-7305

sf-1758745